

REMARKS

The amendments to the claims find support in the specification, for example, at page 5, lines 25-28; page 13, lines 4-6; page 14, lines 1-3; page 24, lines 20-25; page 25, lines 11-17; and elsewhere in the specification and claims as originally filed.

No new matter is added by way of the claim amendments.

Applicants acknowledge the withdrawal of claim rejections under 35 U.S.C. § 112, first paragraph, and the withdrawal of the objection under 35 U.S.C. §132 to the amendment to the specification filed June 18, 2004.

Claims 14-19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 1, 2, 4-6, 8-12, 14, 20, 24-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Chari et al. (U.S. Patent No. 5,208,020, hereafter "Chari") in view of Bacus (U.S. Patent No. 5,514,554, hereafter "Bacus") and further in view of Lewis et al. (Cancer Immunol. Immunotherap. 37:255-263, 1993; hereafter "Lewis").

Claims 1, 2, 8-14, 20, and 24-33 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Huston et al. (U.S. Patent No. 5,877,305, hereafter "Huston") and further in view of Lewis.

Claims 1, 2, 8-12, 24-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of King et al. (U.S. Patent No. 5,747,261, hereafter "King") and further in view of Lewis.

Claims 1, 34, 44 and 45 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak et al. (U.S. Patent No. 5,725,856, hereafter "Hudziak"), Bacus, Huston, or King in view of Lewis as applied to Claim 1 and further in view of Senger et al. (U.S. Patent No. 6,022,541, hereafter "Senger").

Claims 1, 34-37, 42 and 43 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak, Bacus, Huston, or King in view of Lewis as applied to Claim 1 and further in view of Sliwkowski et al. (J. Biol. Chem. 269:14661-14665, 1994; hereafter "Sliwkowski") or Carter.

Claims 1, 4-6, 8-19, 22-25, 27 and 32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Iwassa (U.S. Patent No. 5,217,713, hereafter "Iwassa") in combination with Carter, Hudziak, Bacus, Huston, or King in view of Lewis.

Claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Chari in view of Hudziak and further in view of Lewis.

Claims 55, 2, 4, 5, 8-21, 24-33, 38-41 and 46-48 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Chari in view of Carter (U.S. Patent No. 6,054,297, hereafter "Carter") and further in view of Lewis.

Claims 55, 34, 44, and 45 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Hudziak in view of Lewis, and further in view of Senger.

Claims 55, 34-37, 42, and 43 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Hudziak in view of Lewis, and further in view of Sliwkowski or Carter.

Claims 55, 4-6, 8-19, 24, 25, 27 and 32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Iwassa (U.S. Patent No. 5,217,713, hereafter "Iwassa") in combination with Carter, Hudziak, in view of Lewis.

Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 13-18 of U.S. Patent No. 5,208,020 to Chari et al. in view of Hudziak in view of Lewis.

As discussed in the following remarks, Applicants respectfully traverse the above rejections, and submit that these rejections are rendered moot in view of the claim amendments and arguments presented herein.

The Amendments to the Claims

The amendments to the claims include amendments to Claim 55 which are believed to address the Examiner's concerns as stated in the present Office Action, particularly at pages 7 and 8 of the Office action dated March 17, 2005. For example, referring to the claims as presented prior to the present amendments, the Examiner

suggests that the population discussed in the claims "fails to define a specific subpopulation of patients" (page 7, line 15 of the Office action dated March 17, 2005). The Examiner also suggests that "extrinsic evidence" is lacking "that a population, even if defined as one that responds poorly or not at all to a specific antibody, such as, for example, trastuzumab, would be a population where it would be unexpected that individuals in the population would not respond to maytansinoid-anti-ErbB2 antibody conjugate" and that "it appears that almost any population would respond to a maytansinoid conjugate" (Office Action, page 8, lines 1-6 of the Office action dated March 17, 2005).

First, Applicants note that, as amended, the method of Claim 55 requires "an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells" and thus does not include those antibodies that the Examiner characterized as "not capable of causing any inhibition in cell proliferation" (Office Action dated March 17, 2005, page 7, lines 17-18). Thus, it is not the case that most individuals would be expected to respond poorly or not at all to the antibodies recited in the present claims.

Second, Applicants note that the Examiner's concern regarding the alleged lack of evidence that a subpopulation as defined in the claims would be unexpected that individuals in the population would not respond to maytansinoid-anti-ErbB2 antibody conjugate" (Office Action, page 8, lines 1-5 of the Office action dated March 17, 2005) is addressed by the expert declarations that accompany this response. For example, referring to "HERCEPTIN® non-responding patients," Dr. Lutzker notes that the "observation that these patients continue to over-express HER2 was important and not expected." Dr. Lutzker also stated that "it would not have been obvious to investigate or to determine whether or not a patient fell into that subpopulation of patients." Finally, according to Dr. Lutzker, the information as to whether or not a patient responds poorly, or not at all, to anti-ErbB antibody treatment could be clinically useful.

Applicants have discovered that it may be useful to determine to which population a patient belongs when proposing treatment for that patient. Such a discovery is not obvious, as may be seen, for example, from the Examiner's remarks

indicating a belief that "almost any population would respond to a maytansinoid conjugate" (Office Action dated March 17, 2005, page 8 line 6). Moreover, whether or not one believes that "almost any population would respond to a maytansinoid conjugate," determining the subpopulation to which a patient belongs provides advantages and benefits not available in the absence of the present methods. For example, identification of a patient's subpopulation allows one to tailor a treatment so as to provide an anti-ErbB antibody-maytansinoid conjugate to those patients who require such treatment (those who do not respond to the antibody alone), while being able to spare those patients who do respond to the antibody alone the possible added costs and risks (e.g., of toxicity) of the conjugates. Thus, the present methods requiring identification of a tumor's characteristics are not only not obvious, but provide advantages and benefits that are not available without such identification.

Accordingly, Applicants submit that the present methods define a subpopulation using antibodies that by definition are active, for at least the reason that they have "a growth inhibitory effect on SK-BR-3 cells," that the existence and identification of such a subpopulation was not obvious, and that identification of such a subpopulation provides clinical advantage and benefits. Thus, Applicants submit that the present methods are new, useful, and not obvious.

The Rejections to the Pending Claims Under 35 U.S.C. §112, First Paragraph

Claims 14-19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement, the Examiner suggesting that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, and commenting that the rejection was "a new matter rejection."

Claim 14 has been amended to refer only to SK-BR-3 cells, and not to any of the other cell types previously named in the claim. The Examiner acknowledging the support in the specification for use of the SK-BR-3 cell line (see, e.g., page 5, lines 7-8

of the Office Action under reply), and reference to other cell lines being removed from the claims, Applicants submit that the rejections to Claims 14 and its dependent Claims 15-19 under 35 U.S.C. §112, first paragraph, are overcome.

The Rejections to the Pending Claims Under 35 U.S.C. §103(a)

The Examiner has rejected the pending claims under various combinations of cited references, including apparently maintaining some rejections of canceled Claim 1 (page 2, line 15; page 3, lines 4, 9, 14; page 4, lines 1 and 6). Applicants traverse these rejections, as discussed below in remarks addressed to such rejections in aggregate and in remarks directed to specific rejections enumerated by the Examiner.

The cited references were discussed at length in previous amendments. These prior-filed arguments being hereby incorporated by reference. For the sake of clarity, Applicants summarize the arguments regarding the rejections in an introductory section of this response, in which Applicants' arguments in prior amendments with respect to the claimed invention with regard to the cited references may be summarized but are not repeated.

In addition, Applicants submit two Declarations with this response. One of the Declarants is an inventor of the invention described in the present application, and both Declarants are experts in the field of the invention. These experts base their comments on their training, knowledge and experience in the relevant arts, and discuss how the present application provides unexpected and striking results. As discussed in the following, Applicants submit that the opinions of these experts in the fields of cancer research and cancer treatment confirms the non-obviousness of the Applicants' invention.

As amended, Claim 55 and its dependent claims all recite a treatment method requiring administration to an animal that has a tumor characterized by "the overexpression of an ErbB2 receptor" and by being a tumor "that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells." Moreover, the treatment requires that such a tumor be treated with a conjugate of "an anti-ErbB2

antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells " conjugated together "with a maytansinoid."

In order to establish a *prima facie* case of obviousness, there must be: 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In addition, under 35 U.S.C. §103, each claim must be considered as a whole. As stated by the Federal Circuit in *In re Wright* (838 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988)) "[I]t is the invention as a whole that must be considered in obviousness determinations. The invention as a whole embraces the structure, its properties, and the problem it solves." Similarly, "In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety." *Rockwell International Corp. v. United States*, 47 USPQ2d 1027, 1031 (Fed. Cir. 1998).

When considering the invention as a whole, it is important to note whether, as here, the inventors have identified a problem that was not recognized in the prior art. As stated by the Circuit Court of Patent Appeals in *In re Spinnoble*: "[A] patentable invention may be in the discovery of the source of the problem even though the remedy may be obvious once the source of the problem is identified. This part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." 405 F.2d 578,585, 160 USPQ2d 237,243 (CCPA 1969).

In the section entitled "Response to Arguments," the Examiner notes that the "claimed methods of treatment are directed to a specific population of patients, those that both overexpress ErbB2 receptor and also fail to respond to [*sic*] respond poorly to treatment with an anti-ErbB2 antibody" (page 7, lines 8-10, Office action dated

March 17, 2005). However, the Examiner suggests that "defining the population as one that fails to respond or responds poorly to treatment with an anti-ErbB2 antibody fails to define a specific subpopulation of patients" (page 7, lines 14-15, Office action dated March 17, 2005). The Examiner goes on to suggest that because antibodies "binding to the 4D5 epitope" include hu-Mab4D5-1 and huMab4D5-2 "that are not capable of causing any inhibition in cell proliferation (see Carter, U.S. Patent No. 6,054,297, Table 3, column 53-54) ... most individuals would be expected to respond poorly or not at all to treatment with antibodies such as huMab4D5-1 or huMab4D5-2, which are antibodies that bind to the 4D5 epitope" (page 7, lines 15-20, Office action dated March 17, 2005). The Examiner further suggests that "it appears that almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" (page 8, lines 6-7, Office action dated March 17, 2005).

Thus, it appears that the Examiner's rejections are two-fold. First, the Examiner does not acknowledge the existence of the subpopulation to which the claims are directed; and second, the Examiner suggests that "almost any population would respond to a maytansinoid conjugate," implicitly suggesting that if this might be true, such a supposition would somehow make the present claims obvious. Applicants traverse these rejections.

I. The Existence of the Subpopulation to Which the Claims Are Directed

Applicants have identified a group of tumors that differ from other tumors, including differing from other tumors overexpressing ErbB2 receptors. As discussed below, and as noted by the declarants in the accompanying expert declarations, this subpopulation of ErbB2-overexpressing tumors differs from other ErbB2-overexpressing tumors not only in its response to anti-ErbB2 antibodies, but also differs in its response to anti-Erb2 antibody-maytansinoid conjugates. Thus, the claimed invention is directed to treating an identifiable subpopulation of tumors, and whose response to the claimed treatment with anti-ErbB2 antibody-maytansinoid conjugates is not the same as that of other ErbB2-overexpressing tumors.

The specification provides support for the identification of cells that do not respond, or respond poorly, to anti-ErbB2 antibodies alone; see, for example, Figures 9-14, and the discussion in Example 4 at pages 71-76, which show results regarding tumor cells which do not respond to anti-ErbB2 antibodies alone are shown (e.g., Figure 9).

Further evidence in this regard is provided in the attached Declaration of Dr. M. Sliwkowski, a recognized expert on cancer research and one of the inventors of the present application. For example, as discussed by Dr. Sliwkowski and as disclosed in the figures of the Appendix of Dr. Sliwkowski's Declaration, cells of the CALu 3 cell line respond well to treatment with the anti-ErbB2 antibody HERCEPTIN[®] alone, while cells of the BT474E1 cell line cells respond only poorly to HERCEPTIN[®] alone.

Thus, substantial evidence is provided in the specification and corroborated by further results attested to by an expert declarant that there are cell lines that do respond well to treatment with an anti-ErbB2 antibody alone, and that there are cell lines that do *not* respond well to treatment with an anti-ErbB2 antibody alone. Accordingly, the subpopulation referred to in the claimed invention exists, its existence is supported by substantial evidence, and would be accepted as such by one of ordinary skill in the art.

Furthermore, as discussed by Dr. Stuart Lutzker, a clinical oncologist, in his declaration, such subpopulations are also observed clinically. Dr. Lutzker notes that a recent paper, Spector et al., Jour. of Clin. Onc. 23(11):2502-2512 (2005), discusses the unexpected discovery that HERCEPTIN[®] non-responding patients continue to express or overexpress ErbB. This paper provides further evidence that some tumors that overexpress ErbB may yet not respond to HERCEPTIN[®], as was previously disclosed in the present application and as required by the present claims. Dr. Lutzker states that "[p]rior to this recent observation, it would not have been obvious to investigate or to determine whether or not a patient fell into that subpopulation of patients." Moreover, Dr. Lutzker is of the opinion that such information could be clinically useful, and further stated that "it would be helpful in my clinical practice to have available treatment methods to help those patients whose cancers overexpress ErbB2 yet who do not seem to be helped by anti-ErbB antibody treatment."

Identification of a Problem in the Art

When considering the invention as a whole, as recognized by the Circuit Court of Patent Appeals in *In re Spinnoble* (Id.), it is important to note whether the inventors have identified a problem that was not recognized in the prior art. Applicants submit that they have identified a problem that was not recognized in the prior art, and have provided a solution to that problem.

II. The Effect of Maytansinoid Conjugates on the Subpopulation

The specification provides support for the discovery that there are cells that do not respond, or respond poorly, to anti-ErbB2 antibodies alone that do, however, respond to treatment with anti-ErbB2 antibody-maytansinoid conjugates; see, for example, Figures 9-14, and the discussion in Example 4 at pages 71-76, in which tumor cells which do not respond to anti-ErbB2 antibodies alone are shown to respond to treatment with anti-ErbB2 antibody-maytansinoid conjugates (e.g., Figure 9).

Thus, the specification provides evidence supporting the response of the subpopulation of cells recited in the claims. Such response provides further evidence that these cells fall into a different subpopulation than other cells that respond to anti-ErbB2 antibodies alone.

Moreover, as discussed by Dr. Sliwkowski and supported by evidence provided by Dr. Sliwkowski in the attached declaration, the different subpopulations of cells respond differently to anti-ErbB2 antibody-maytansinoid conjugates. Such different response is further evidence of the existence of, and differences between, the subpopulations. In addition, the different responses to treatment with anti-ErbB2 antibody-maytansinoid conjugates makes it critical to determine into which subpopulation a tumor falls in determining dosing and treatment for that tumor.

As noted in Dr. Sliwkowski's declaration, CALu 3 cells respond well to HERCEPTIN[®] alone; and CALu 3 cells also respond well to conjugates of HERCEPTIN[®]-maytansinoid: a conjugate dose of 165 μ g/kg DM1 gave a complete response. Inspection of the results provided in Figure 1 of the Sliwkowski declaration

indicate that even a lesser dose may have been sufficient for a complete response, as the effect appears to be maximal at that dose.

However, BT474E1 cells respond, if at all, only poorly to HERCEPTIN[®] alone. The BT474E1 cells do respond to conjugates of HERCEPTIN[®]-maytansinoid. However, it took a 50% larger dose than required by the CALu 3 cells (250 $\mu\text{g/kg}$ HERCEPTIN[®]-DM1) to get a nearly complete response. Note that this response was not a maximal response, so that an even higher dose would be required to achieve the same response as was obtained by 165 $\mu\text{g/kg}$ HERCEPTIN[®]-DM1 treatment of CALu-3 cells.

Thus, the subpopulation of tumor cells that do not respond or that respond poorly to HERCEPTIN[®] alone also responds more poorly to HERCEPTIN[®]-DM1 conjugates than does a cell line that responds well to HERCEPTIN[®] alone. This difference in response further identifies these groups as being different from each other (*i.e.*, being two different identifiable populations) and identification of these subpopulations has important implications for the successful treatment of tumors from these two groups.

All Steps Must Be Taken Into Account in Determining Non-Obviousness

It is clear from the different responses of these cells, and in particular the different dosages required for complete response to treatment, that determining which population a tumor belongs to (step (i) of the claimed method) may be critical in determining the treatment by anti-ErbB2 antibody-maytansinoid conjugates (step (ii) of the claimed methods).

Thus, in contrast to the Examiner's suggestion that "almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" (page 8, lines 6-7, Office action dated March 17, 2005) the claimed methods provide an effective, and more targeted, method for treating tumors that overexpress ErbB2 receptors.

Identifying the population of tumors characterized as required by the claimed invention allows one to treat the tumors selected in the claimed method with the proper effective therapeutic dose of antibody-maytansinoid conjugate. This proper dose differs

from that which would be optimal for a tumor cell that does not satisfy the selection criteria required by the claimed invention. Determination of the type of tumor being treated provides information that allows one to provide the treatment appropriate to the cells being treated, and is not a superfluous or irrelevant step.

Applicants note that merely increasing the dose of anti-ErbB2 antibody-maytansinoid conjugates for all patients, in order to avoid determining which population a tumor to be treated belongs to, is not a viable alternative, for at least the reasons that the anti-ErbB2 antibody-maytansinoid conjugates are expected to have toxic side effects that a physician must try to minimize, and that anti-ErbB2 antibody-maytansinoid conjugates, like all drugs, will have costs associated with them that a patient (or patient's insurance plan), if not the physician, will try to minimize. Thus, the step (i) of determining which population a tumor to be treated belongs to is an effective and integral part of the claimed methods, and must be considered in any determination of the non-obviousness of the claimed invention.

Thus, not only does the prior art fail to suggest determining to which of the subpopulations a tumor belongs, and fail to recognize the usefulness of such a determination, but moreover no reference and no combination of references teaches the claimed method comprising both the above steps. No reference or combination of references suggests, or would motivate one of ordinary skill in the art to perform these steps as claimed. Indeed, this lack of suggestion or motivation is implicitly acknowledged by the Examiner, since if it were true, as suggested by the Examiner (page 8, lines 6-7, Office action dated March 17, 2005), that "it appears that almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" then there would be no suggestion or motivation in the art to perform the step (1) above, and no suggestion or motivation to provide the claimed invention comprising all the claimed steps.

The Federal Circuit in *In re Zurko* stated that :

"[T]o say that the missing step comes from the nature of the problem to be solved begs the question because the Board has failed to show that this problem had been previously identified anywhere in the prior art. see *In re Spinnable* 405 F.2d 578, 585, 160 USPQ 237, 243

(CCPA 1969) ("[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.')." *In re Zurko* 42 USPQ2d 1476, 1479 (Fed Cir. 1997) *rehearing en banc granted*, 116 F.3d 874 (Fed. Cir. 1997)

The present invention identifies and provides a solution to a problem that was not recognized in the art. The claimed invention is directed to treating a tumor in a mammal that is characterized by overexpression of an ErbB2 receptor and that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells. No cited art identifies such tumors as targets for treatment, nor do any cited references provide a treatment directed to such tumors.

As indicated by the Examiner's rejections, it was not obvious that identification of the subpopulation of tumors to be treated would provide any benefit or would identify tumors treatable by the treatments recited in the claimed methods. Instead, one of ordinary skill in the art would have assumed, as stated by the Examiner, that "almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" and so would find the claimed invention surprising and not obvious.

Failing to identify the such target tumors, and failing to provide any treatments directed to such tumors, no combination of any of the cited references provides the invention as a whole as recited in the pending claims, nor would suggest these claims, nor would provide any reasonable expectation of success for these claims. For example, although the claimed invention requires determination that a tumor to be treated have been determined to not respond, or to respond poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells, no reference and no combination of references discusses or suggests this element of the claims. This element is effective, as discussed in the declaration accompanying this paper, at least for the reason that the effective amount of anti-ErbB antibody-maytansinoid conjugate required by such cells is different than the effective amount of anti-ErbB antibody-maytansinoid conjugate required by cells that do respond to anti-ErbB antibody alone.

The pending claims as a whole are directed to inventions which are not found and not suggested in the prior art, and which are not provided by any combination of the cited references. Accordingly, Applicants submit that the claims, when viewed in the light of the above criteria, are not obvious over the cited references.

The Invention as a Whole Need Not Provide the "Best" Alternative

Moreover, "The Federal Circuit stated that a finding that "an invention that is an 'improvement' is not a prerequisite to patentability" since it "is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability." (*Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 1 USPQ2d 1196 (Fed. Cir. 1986))."

As noted above, the Examiner has suggested that "it appears that almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" (page 8, lines 6-7, Office action dated March 17, 2005). Applicants note that the present invention provides an effective method for treating a tumor in a mammal, one that requires the identification of a characteristic of a tumor to be treated that is important in determining the treatment of that tumor. Thus, even if the Examiner's suggestion were true, it does not negate the non-obviousness of the present invention. Accordingly, Applicants submit that regardless of whether or not "almost any population would respond to a maytansinoid conjugate" the present invention provides a non-obvious method for treating a tumor in a mammal.

None of the cited references discusses or suggests, and no combination of the cited references discusses or suggests determining that a tumor does not respond, or responds only poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope. Thus, no combination of the cited references provides or suggests this claim element. Moreover, none of the cited references discuss or suggest, and no combination of the cited references discusses or suggests, a treatment for such a tumor with a conjugate of a maytansinoid with an anti-ErbB2 antibody which binds to the 4D5

epitope. Thus, no combination of the cited references provides or suggests this additional claim element.

Moreover, the Examiner provided no specific reasons why the references cited, or the prior art as a whole, would have provided any motivation to make this invention. In fact, Applicants submit that the Examiner's comment quoted above is a further indication that the prior art provides *no* motivation to provide the determining step. Motivation to combine the cited references must come from the prior art references themselves, and not as a result of hindsight. *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). "[A] retrospective view of inherency is not substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

Lacking any such discussion or suggestion, the cited references, however combined, provide no reasonable expectation of success for the claimed methods. Moreover, as discussed above and in the attached declarations, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to provide all elements of the claimed invention; since 2), the cited references fail to suggest or to motivate the combination of such elements in an attempt to provide the claimed methods; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5) the present invention provides unexpected results; and for other reasons, Applicants respectfully submit that Claims 2, 4-6, 8-21, 24-48, and 55 are not made obvious by the cited references and that the claim rejections under 35 U.S.C. §103(a) are overcome.

III. The Maytansinoid Conjugates are not Obvious

Applicants further note that the claimed conjugates and treatment methods are not obvious since one of ordinary skill in the art would not be led to prepare the conjugates of the present claims nor be led to the claimed treatment methods. As noted by Chari in discussing antibody drug conjugates such as antibody-targeted

methotrexate, antibody-targeted vinblastine, and antibody-targeted doxorubicin, "in clinical trials conducted so far, early antibody-drug conjugates have failed to live up to the promise of the targeted delivery approach for the treatment of cancer" (page 96, column 1, "Targeted delivery of chemotherapeutics: tumor-activated prodrug therapy," Advanced Drug Delivery Reviews 31:89-104 (1998)). Thus, the Examiner's statement "it appears that almost any population would respond to a maytansinoid conjugate" (page 8, line 6, Office Action dated March 17, 2005) is not in accordance with the expectations of one of skill in the art at the time of the application.

In addition to the above, and in addition to all prior Amendments (including the amendments mailed on July 30, 2002; February 24, 2003; November 3, 2003 and as corrected on December 10, 2003; June 18, 2004; and November 9, 2004) filed in response to previous Office Actions (the arguments presented therein being hereby incorporated by reference) Applicants present arguments below directed to the specific claim rejections under 35 U.S.C. §103(a) as made or maintained by the Examiner in the present Office Action.

The 35 U.S.C. §103(a) Rejections to Claims 1, 2, 4-6, 8-12, 14, 20, 24-33, and 38-41

Claims 1, 2, 4-6, 8-12, 14, 20, 24-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Chari in view of Bacus (U.S. Patent No. 5,514,554, hereafter "Bacus") and further in view of Lewis.

Obviousness under 35 U.S.C. §103(a) requires several elements, and may not be directed by hindsight based on the disclosure under examination. Thus, the Federal Circuit has stated that:

"In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure." In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Chari is presented by the Examiner as providing maytansinoid compounds (including maytansinol, maytansine, and maytansinol esters including DM1) attached to monoclonal antibodies or their fragments, and as providing methods of killing selected cell populations.

Bacus is presented as providing anti-ErbB2 antibodies that are growth inhibitory, induce cell death, and that induce apoptosis, and that such antibodies may be conjugated to cytotoxic moieties.

Chari and Lewis are presented by the Examiner as discussed above, the Examiner stating that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody" (page 8, lines 11-12). Bacus is presented as providing anti-ErbB2 antibodies that are growth inhibitory, induce cell death, and that induce apoptosis, and that such antibodies may be conjugated to cytotoxic moieties. Applicants respectfully submit that Claims 1, 2, 4-6, 8-12, 14, 20-33, and 38-41 are not obvious under 35 U.S.C. §103(a) over the cited references.

Although the Examiner suggests that Lewis "teaches that some tumor cells that overexpress ErbB2 fail to respond to murine antibody 4D5" (page 5, lines 9-10 of the Office Action dated March 26, 2004), Applicants note that Lewis nowhere suggests methods for treating such tumors, and in particular, Lewis nowhere suggests treating such tumors with maytansinoids conjugated to those particular antibodies which Lewis showed did not inhibit the growth of such cells. Lewis provides no teaching, no suggestion, and no motivation to determine whether a tumor does not respond, or responds poorly, to anti-ErbB2 antibody and then to provide the conjugate treatment as required by the present claims.

In fact, Lewis teaches away from the methods of the present invention. Lewis states that "The sensitivity of breast tumor cell lines to antibody-mediated growth inhibition correlates well with their level of p185^{HER2} overexpression." (page 261, column 2, lines 27-30). Lewis thus teaches that cells that overexpress p185^{HER2} can be treated with anti-ErbB2 antibodies alone. Lewis does not explain the discrepancy between their main conclusion (that antibody-sensitivity increases with increasing p185^{HER2} overexpression) and their observation that some cells fail to respond to anti-ErbB2

antibodies. Lewis further fails to provide any hypothesis or suggestion to explain the existence of such non-responding cells. Moreover, Lewis also fails to suggest a possible treatment for such non-responding cells, and provides no basis for suggesting a possible treatment.

There is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Like Lewis, Bacus also lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. As noted by the Examiner, Chari fails to teach conjugates comprising anti-ErbB2 antibodies. Applicants note that Chari also fails to discuss tumors that fail to respond, or respond poorly, to antiErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Bacus also fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Bacus). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. Applicants respectfully submit that Claims 1, 2, 4, 5, 8-12, 20-33, and 38-41 are not obvious under 35 U.S.C. §103(a) over the cited references.

The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by

hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, lacking any teaching or suggestion of elements of the claimed invention, and failing to provide an expectation of success were such such elements to be combined, Applicants submit that the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails and respectfully submit that Chari, in view of Bacus and in view of Lewis fail to make Claims 1, 2, 4-6, 8-12, 14, 20-33 and 38-41 obvious.

The 35 U.S.C. §103(a) Rejections to Claims 1, 2, 8-14, 20, and 24-33

Claims 1, 2, 8-14, 20, and 24-33 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Huston and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above, the Examiner stating that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments) and neither Chari nor Lewis teach methods for treatment of metastatic breast cancer." (page 9, lines 13-15, Office Action dated March 26, 2004). Huston is presented as providing single-chain Fv that bind to ErbB2, and methods of treating cancer comprising linking the Fv to an agent that can limit tumor proliferation, and methods for treating metastatic breast cancer (page 9, lines 17-21). Applicants respectfully submit that Claims 1, 2, 8-14, and 20-33 are not obvious under 35 U.S.C. §103(a) over Chari, Lewis and Huston.

Lewis and Huston each lack disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

Huston fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, neither Chari nor

Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts, as discussed above. Accordingly, the cited references either teach away from, or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Huston). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 10, lines 3-6 of the Office Action dated March 26, 2004, emphasis added). The Examiner notes that Huston contemplated the use of single-chain Fv linked to a therapeutic agent, (page 10, lines 6-7 of the Office Action dated March 26, 2004) and suggests that since Huston discusses such Fv conjugates and since Lewis noted some ErbB2 overexpressing cells failed to respond to anti-ErbB2 antibodies, "one would have been motivated to use the antibodies of Huston to make the maytansinoid conjugates" (page 10, lines 10-13 of the Office Action dated March 26, 2004).

However, Huston, which does not mention maytansinoid compounds, nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and provides no suggestion of such treatments. Huston also fails to discuss or even suggest treatments of tumors that overexpress ErbB2 yet do not respond, or respond

poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss determining whether a tumor does not respond, or responds poorly, to anti-ErbB2 antibody treatment as part of a method for treating those having such tumors; none discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis fails to suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

As discussed above, Applicants note that the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness, "obvious to try" not being equated with obviousness under 35 U.S.C. §103.

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and Huston fail to discuss, or suggest, the present methods or to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, applicants respectfully submit that Chari, in view of Huston and in view of Lewis fail to make Claims 1, 2, 8-14, 20-33 obvious.

The 35 U.S.C. §103(a) Rejections to Claims 1, 2, 8-12, 24-33, and 38-41

Claims 1, 2, 8-12, 24-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of King and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above, the Examiner stating that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments)." (page 10, lines 19-120). King is

presented as providing methods for treating cancer that express high levels of ErbB2, using antibodies to ErbB2 linked to agents that are toxic to cells (page 11, lines 1-4). Applicants respectfully submit that Claims 1, 2, 8-12, 22-33 and 38-41 are not obvious under 35 U.S.C. §103(a) over Chari, Lewis and King.

Lewis and King each lack disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

King fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and King). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 11, lines 7-10 of the Office Action dated March 26, 2004, emphasis added). The Examiner notes that King contemplated the use of an antibody linked to one or more agents that will cause injury to cells (page 11, lines 10-12 of the Office Action dated March 26, 2004) and suggests that since King discusses such antibodies linked to cell-toxic agents, and since Lewis noted some ErbB2 overexpressing cells failed to respond to anti-ErbB2 antibodies, "one would have been motivated to use the antibodies of King to make the maytansinoid conjugates" (page 11, lines 15-16 of the Office Action dated March 26, 2004).

However, King, which does not mention maytansinoid compounds, nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and provides no suggestion of such treatments. King does not discuss or even suggest treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis fails to suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

As discussed above, Applicants note that the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness, "obvious to try" not being equated with obviousness under 35 U.S.C. §103.

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As

discussed above, Lewis teaches away from the claimed methods, and Chari and King fail to discuss, or suggest, the present methods or to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5), the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that Chari, in view of King and in view of Lewis fail to make Claims 1, 2, 8-12, 22-33, and 38-41 obvious.

The 35 U.S.C. §103(a) Rejections to Claims 1, 34, 44, and 45

Claims 1, 34, 44 and 45 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak, Bacus, Huston, or King in view of Lewis as applied to Claim 1 and further in view of Senger.

Hudziak is presented by the Examiner to provide anti-ErbB2 antibodies and fragments, including growth inhibitory and cytotoxic anti-ErbB2 antibodies. As mentioned above, the Examiner acknowledges that Hudziak fails to teach “that the patient has not responded or responded poorly to an unconjugated anti-ErbB2 antibody” (page 5, lines 6-8 of the Office Action dated March 26, 2004).

Lewis is presented by the Examiner as discussing tumor cells that overexpress ErbB2 and fail to respond to murine antibody 4D5 by exhibiting growth inhibition.

Chari, Hudziak, Huston, King and Lewis are presented by the Examiner as discussed above. The Examiner characterizes Claims 1, 34, 44 and 45 as drawn to treatment methods comprising administration of a maytansinoid conjugated to an antibody that binds ErbB2, and a second antibody that may be conjugated to any

cytotoxic agent (page 12, lines 3-6). The Examiner states that Chari with Hudziak or Bacus or Huston or King fail to teach methods using combinations of at least two antibodies. Senger is presented to discuss treatment of tumors using at least two antibodies that bind to vascular permeability factor (VPF) and which may be conjugated to a toxin (page 12, lines 11-14).

However, except for Chari, all the cited references lack disclosure of maytansinoids, or of antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari and Senger lack any disclosure or suggestion of anti-ErbB2 antibodies. No relation between VPF and ErbB2 or between VPF antibodies and maytansinoids is suggested. Although the Examiner presents Senger as providing an example of a treatment strategy where an antigen is targeted with two different antibodies, where each antibody is conjugated with a toxin, there is no link apparent, and the Examiner provides no explanation for a link, between VPF and tumors which overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

The cited references also fail to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, Lewis actually teaches away from such treatments. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody.

The Examiner suggests that "because Senger provides an example of a treatment strategy where an antigen is targeted with two different antibodies, where each are conjugated to a toxin" (page 12, line 21 to page 13, lines 1-2), it would have been obvious to combine Chari with either of Bacus, Huston or King in view of Lewis. However, none of these references suggests or motivates such a combination, the

references fail to teach a relationship between anti-VPF antibodies, treatments with such antibodies, and the present methods, and none of the cited references suggests or motivates methods of treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

Failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness. Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 3), the cited references provide no reasonable expectation of success were the references to be so combined; since 4), the present invention provides unexpected results; and for other reasons discussed above, Applicants respectfully submit that the rejections of Claims 1, 34, 44 and 45 under 35 U.S.C. §103(a) are overcome.

The Rejections to Claims 1, 34-37, 42 and 43 Under 35 U.S.C. §103(a)

Claims 1, 34-37, 42 and 43 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in combination with Hudziak, Bacus, Huston, or King in view of Lewis as applied to Claim 1 and further in view of Sliwkowski et al. (J. Biol. Chem. 269:14661-14665, 1994; hereafter "Sliwkowski") or Carter.

Chari, Hudziak, Bacus, Huston, King and Lewis have been discussed above. Sliwkowski is presented as discussing an anti-ErbB2 antibody, 2C4, that "may be used to inhibit the binding of heregulin (a growth factor) to ErbB3" and Carter is presented as discussing that "huMab4D5-8 acts to recruit immune effector cells to a tumor" (page 13, lines 17-20, Office Action dated March 26, 2004). The Examiner suggests that it would be obvious to rely on these references for the use of a second antibody to block the effects of a growth factor or to recruit immune effector cells to a tumor, citing *in re Kerkhoven* to suggest that the combination of two elements known to be useful for one purpose, to provide a third composition for that purpose.

The Examiner states that "In the instant case the first therapeutic composition is the anti-ErbB3-maytansinoid conjugate" (page 14, lines 9-10 of the Office Action dated March 2, 2004). However, none of the references, including neither Sliwkowski nor Carter, discuss treatment of a tumor in a mammal where that tumor overexpresses ErbB2 and that tumor also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Such treatments are an important purpose of the present invention, and the purpose of the present claims. The cited references thus do not discuss a purpose of the claimed invention. For at least this reason, it is not clear how *in re Kerkhoven* applies to the present rejections.

In addition, as discussed above, such a therapeutic composition is not obvious over any combination of the cited references; the claimed therapeutic methods are not suggested not motivated by the cited references. However, as acknowledged by the Examiner, an *in re Kerkhoven* analysis requires that "each of the two compositions is taught by the prior art to be useful for the same purpose" (page 14, lines 7-8 of the Office Action dated March 26, 2004). As discussed above, the conjugates of the claimed methods are not taught by the prior art; nor are they suggested by the prior art; nor does any reference or combination of references suggest the purpose of the methods of the present claims. Thus, there is no basis in the art for the sort of *in re Kerkhoven* analysis suggested by the Examiner, nor would such an analysis provide the methods of the present claims, lacking both the compositions and the purpose for which

those compositions are applied (to treat tumors in an mammal that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody).

Moreover, the present disclosure provides unexpected results. The target tumors of the present invention are those that do not respond, or respond poorly to anti-ErbB2 antibodies, so that treatments based on these antibodies would not be expected to be work. Surprisingly, the present inventors have shown that anti-ErbB2 antibodies conjugated with maytansinoids are useful in treating tumor cells that do not respond, or respond poorly to anti-ErbB2 antibodies. As discussed in *in re Kerkhoven*, it appears that one may refute an allegation of obviousness where inventors show superiority over the cited references (see, e.g., page 1973, column 1, lines 3-10, discussing Kerkhoven's failure to do so). Thus, for this reason as well, Applicants submit that Claims 1, 34-37, 42 and 43 are not obvious over the cited references.

The cited references thus fail to suggest or motivate a combination to provide the claimed methods, and provide no reasonable expectation of success for such a combination, since no reference discusses any method of treating the target tumor population. Moreover, as discussed above, the present specification discloses unexpected results. Accordingly, applicants submit that the rejections of Claims 1, 34-37, 42 and 43 under 35 U.S.C. §103(a) are overcome.

The 35 U.S.C. §103(a) Rejections to Claims 1, 4-6, 8-19, 22-25, 27 and 32

Claims 1, 4-6, 8-19, 22-25, 27 and 32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Iwassa in combination with Carter, Hudziak, Bacus, Huston, or King in view of Lewis.

Carter, Hudziak, Bacus, Huston, King and Lewis are presented by the Examiner as discussed above. Iwassa is presented by the Examiner as providing an immunocomplex that comprises a bispecific antibody that binds to a tumor antigen and to a maytansinoid. The Examiner also states that Iwassa "fails to teach that the immunocomplex binds to the ErbB2 tumor antigen" (page 15, lines 5-6 of the Office Action dated March 25, 2004). Applicants note that Iwassa also fails to suggest targeting tumors that overexpress the ErbB2 tumor antigen and also fail to respond, or

only respond poorly, to anti-ErbB2 antibodies. The Examiner cites Carter, Hudziak, Bacus, Huston and King as discussing that the ErbB2 tumor antigen is useful for targeting, and Lewis as discussing that some tumor cells that overexpress ErbB2 fail to respond to anti-ErbB2 antibodies. However, the cited references nowhere suggest targeting a tumor for treatment with anti-ErbB2 antibodies conjugated with maytansinoids where that tumor is known not to respond to such anti-ErbB2 antibodies.

Thus, there being no suggestion to combine the cited references in those references themselves, such a suggestion must come from the present disclosure, and so be based on impermissible hindsight, or arise out of a belief that it might have been obvious to try such a combination. However, as discussed above, "obvious to try" may not be equated with obviousness under 35 U.S.C. §103.

As discussed above the cited references provide no suggestion or motivation to provide a treatment for such target tumors and provide no suggestion or motivation for treating such target tumors with anti-ErbB2 antibodies conjugated with maytansinoids. Iwassa does not make up for this lack of suggestion or motivation, not discussing ErbB2, nor anti-ErbB2 antibodies, and nowhere discussing or suggesting targeting tumors which overexpress ErbB2 yet do not respond to anti-erbB2 antibodies. Failing this, Iwassa and the other cited references fails to provide any reasonable expectation of success for such a combination.

Moreover, as discussed above, the present results are surprising and unexpected.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 3), the cited references provide no reasonable expectation of success were the references to be so combined; since 4), the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that the rejections of Claims 1, 4-6, 8-19, 22-25, 27 and 32 under 35 U.S.C. §103(a) are overcome.

The 35 U.S.C. §103(a) Rejections to Claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41

Claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Chari in view of Hudziak and further in view of Lewis.

Chari is presented by the Examiner as providing maytansinoid compounds (including maytansinol, maytansine, and maytansinol esters including DM1) attached to monoclonal antibodies or their fragments, and as providing methods of killing selected cell populations. Hudziak is presented by the Examiner to provide anti-ErbB2 antibodies and fragments, including growth inhibitory and cytotoxic anti-ErbB2 antibodies. Lewis is presented by the Examiner as discussing tumor cells that overexpress ErbB2 and fail to respond to murine antibody 4D5 by exhibiting growth inhibition.

As noted by the Examiner, Chari fails to teach conjugates comprising anti-ErbB2 antibodies. The Examiner also notes that Hudziak fails to teach "that the patient has not responded or responded poorly to an unconjugated anti-ErbB2 antibody" (page 5, lines 6-8 of the Office Action dated March 26, 2004). Applicants note that Chari also fails to discuss tumors that fail to respond, or respond poorly, to anti-ErbB2 antibodies. Applicants respectfully submit that Claims 55, 2, 4, 5, 8-12, 20-33, and 38-41 are not obvious under 35 U.S.C. §103(a) over the cited references.

Cited References Fail to Provide any Suggestion or Motivation to Combine

Applicants respectfully submit that there is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Hudziak and Lewis each fail to disclose and fail to suggest maytansinoid compounds. Thus, there is no link between these references apart from the present disclosure. Although the Examiner suggests that Lewis "teaches that some tumor cells that overexpress ErbB2 fail to respond to murine antibody 4D5" (page 5, lines 9-10 of the Office Action dated March 26, 2004), Applicants note that Lewis nowhere suggests

methods for treating such tumors, and in particular, Lewis nowhere suggests treating such tumors with maytansinoids conjugated to those particular antibodies which Lewis showed did not inhibit the growth of such cells.

In fact, Lewis teaches away from the methods of the present invention. Lewis states that "The sensitivity of breast tumor cell lines to antibody-mediated growth inhibition correlates well with their level of p185^{HER2} overexpression." (page 261, column 2, lines 27-30). Lewis thus teaches that cells that overexpress p185^{HER2} can be treated with anti-ErbB2 antibodies alone. Lewis does not explain the discrepancy between their main conclusion (that antibody-sensitivity increases with increasing p185^{HER2} overexpression) and their observation that some cells fail to respond to anti-ErbB2 antibodies. Lewis further fails to provide any hypothesis or suggestion to explain the existence of such non-responding cells. Moreover, Lewis also fails to suggest a possible treatment for such non-responding cells, and provides no basis for suggesting a possible treatment.

Moreover, Chari and Hudziak each also fail to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from, or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention.

The cited references fail to provide motivation to be so combined and fail to provide such a suggestion. Thus, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

As stated by the Federal Circuit: "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one or ordinary

skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. ... Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight.” In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999).

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that “In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid.” (page 5, lines 14-17 of the Office Action, emphasis added). However, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the cited references provide any motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population.

Applicants respectfully note that the question of whether or not it would have been surprising that such a population of patient exists is not the proper standard for presenting a case for obviousness. Since none of the cited references suggests or motivates combination with the other cited references to provide the claimed methods using anti-ErbB2 antibodies conjugated to maytansinoids, the Examiner's suggestion that it would not have been surprising if a population existed that did not respond to treatments that differ from the claimed treatment methods does not support a *prima facie* case of obviousness. The Federal Circuit has stated that “obvious to try is not the standard” *Ecolchem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 56 USPQ2d 1065 (Fed Cir. 2000) and that “we have consistently held that ‘obvious to try’ is not to be equated with obviousness under 35 U.S.C. §103.” *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

For this reason as well, Applicants respectfully submit that Chari, in view of Hudziak and in view of Lewis fail to make Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 obvious.

As noted above, the Examiner stated that "In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 5, line 14-17 of the Office Action, emphasis added). The basis for the underlined portion of the Examiner's statement is unclear, since none of the references discuss an anti-ErbB2 antibody that was conjugated to a maytansinoid. It appears that the only suggestion for treatment of such tumors with an anti-ErbB2 antibody conjugated to a maytansinoid is derived from the present specification. As discussed above, hindsight is improper and may not be used to support a case for obviousness.

The Examiner also suggests that "the prior art recognized that an anti-ErbB2 antibody could be used for the purpose of delivering a cytotoxic moiety to a tumor, especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2" (page 6, lines 10-12 of the Office Action dated March 26, 2004). However, no cited reference discusses or suggests using an anti-ErbB2 antibody to deliver a cytotoxic moiety to a tumor; thus the basis for the statement above is obscure. In addition, there is no teaching or suggestion in the cited references that an anti-ErbB2 antibody could be used to deliver a cytotoxic moiety especially to tumors that do not respond to the ErbB2 antibody alone. This statement as well is not believed to be supported by the cited references. Thus, for these reasons as well, Applicants respectfully submit that the prior art does not suggest the present methods nor suggest that the cited references be combined to provide the claimed methods.

Cited References Fail to Provide a Reasonable Expectation of Success

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. In fact, Applicants respectfully submit that Lewis teaches away from the claimed methods by

stating that, although for most cells "The sensitivity of breast tumor cell lines to antibody-mediated growth inhibition correlates well with their level of p185^{HER2} overexpression." (page 261, column 2, lines 27-30) Lewis notes that some cells do not respond in this way. One of ordinary skill in the art would thus expect that, for those cells that do not respond, or respond poorly, to anti-ErbB2 antibodies (*i.e.*, for which the antibody treatment fails), other treatments based on such antibodies would also fail. Thus, being taught by Lewis that such antibody treatments would likely fail, and Chari and Hudziak also failing to provide reason to expect success in treating the target cell population, the combination of the cited references fails to provide a reasonable expectation of success.

Accordingly, since 1) the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; and for other reasons discussed above, Applicants respectfully submit that Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 are not made obvious by the cited references.

Moreover, the present specification reports unexpected results. As discussed above, Lewis teaches that most cells that overexpress ErbB2 are susceptible to treatment by anti-ErbB2 antibodies, and that there are also some cells which do not respond to such antibodies. Surprisingly, the present inventors discovered methods for treating such non-responding, or poorly responding, cells using modified anti-ErbB2 antibodies – the same antibodies that were shown in the art not to affect such cells. Such unexpected results further illustrate that Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 are not obvious over the cited references.

The 35 U.S.C. §103(a) Rejections to Claims 55, 2, 4, 5, 8-12, 24-33, 38-41, and 46-48

Claims 55, 2, 4, 5, 8-21, 24-33, 38-41 and 46-48 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Chari in view of Carter and further in view of Lewis.

Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Carter and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above. Carter is presented as providing humanized 4D5 antibodies, and in addition is said by the Examiner to teach each of huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8. Applicants respectfully submit that Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 are not obvious under 35 U.S.C. §103(a) over the cited references.

As discussed above regarding the rejections of Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 over Chari, Hudziak and Lewis, there is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Chari and Lewis are also cited in the present rejections of Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48. Carter is cited in place of Hudziak. However, like Hudziak and Lewis, Carter also lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Carter also fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody.

Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Carter). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention.

The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Applicants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that “In view of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid.” (page 7, lines 17-19 of the Office Action, emphasis added). The Examiner notes that Carter contemplated the use of immunotoxins in methods of treatment (page 7, lines 19-20 of the Office Action dated March 26, 2004) and suggests that since Carter discusses ErbB2 and since Lewis noted some ErbB2 overexpressing cells failed to respond to anti-ErbB2 antibodies, “one would have been motivated to use the antibodies of Carter to make the maytansinoid conjugates” (page 8, lines 1-5 of the Office Action dated March 26, 2004).

However, Carter nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and nowhere contemplates treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss such a population of patients as a target for treatment; none suggest treatments for such a population of patients; none of the references suggest treatment of such patients with maytansinoid conjugates, nor do any of the

cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis does not suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

As discussed above, the question of whether or not it would have been surprising that such a population of patient exists is not that the proper standard for presenting a case for obviousness. Applicants again respectfully note that the Federal Circuit has stated that "we have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. §103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and Carter fail to discuss or to suggest the present methods and fail to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5), the present invention provides unexpected results; and for other reasons discussed above, applicants respectfully submit that Chari, in view of Carter and in view of Lewis fail to make Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 obvious.

The 35 U.S.C. §103(a) Rejections to Claims 55, 34, 44, and 45

Claims 55, 34, 44, and 45 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Hudziak in view of Lewis, and further in view of Senger.

As discussed above, neither Chari, nor Hudziak, nor Lewis suggest or motivate one to determine whether a tumor does not respond, or responds poorly, to anti-ErbB2 antibody, and then to provide an anti-ErbB2 antibody-Maytansinoid conjugate to treat such a tumor. Senger also fails to provide such teachings or motivation.

Senger is directed to an "immunological preparation comprising not less than two types of conjugate molecules in admixture for concurrent specific binding to a spatially exposed region of vascular permeability factor (VPF) bound in-vivo to a tumor-associated blood vessel" (Senger Abstract). However, Senger does not discuss ErbB2, anti-ErbB2 antibodies, nor tumors which do not respond, or respond only poorly, to anti-ErbB2 antibodies. Moreover, Senger nowhere discusses antibody-Maytansinoid conjugates. Senger fails to provide any of the missing teachings lacking from the combination of Chari in view of Hudziak in view of Lewis. Senger also fails to provide any motivation to determine whether or not a tumor does not respond, or responds only poorly, to anti-ErbB2 antibodies, or to use an anti-ErbB2-Maytansinoid conjugate to treat such tumors. In addition, Senger provides no expectation of success for such a combination were one to provide it even in view of the lack of motivation or suggestion to do so.

Accordingly, the combination of these references failing to provide all the elements of the claimed invention, and failing to provide any motivation to be combined, or expectation of success were they to be so combined, and for other reasons discussed above, applicants respectfully submit that Chari in view of Hudziak in view of Lewis, and further in view of Senger fail to make Claims 55, 34, 44, and 45 obvious.

The 35 U.S.C. §103(a) Rejections to Claims 55, 34-37, 42, and 43

Claims 55, 34-37, 42, and 43 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Hudziak in view of Lewis, and further in view of Sliwowski or Carter. In view of the fact that Claim 1 has been canceled and

Claims 34-37, 42 and 43 amended to depend from Claim 55, the arguments presented above with respect to the (maintained) rejections to Claims 1, 34-37, 42 and 43 are hereby reiterated with respect to the rejections of Claims 55, 34-37, 42, and 43 under 35 U.S.C. §103(a).

Accordingly, applicants submit that the rejections of Claims 55, 34-37, 42 and 43 under 35 U.S.C. §103(a) are overcome.

The 35 U.S.C. §103(a) Rejections to Claims 55, 4-6, 8-19, 24, 25, 27, and 32

Claims 55, 4-6, 8-19, 24, 25, 27 and 32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Iwassa (U.S. Patent No. 5,217,713, hereafter "Iwassa") in combination with Carter, Hudziak, in view of Lewis.

In view of the fact that Claim 1 has been canceled and Claims 4-6, 8-19, 24, 25, 27 and 32 amended to depend from Claim 55, the arguments presented above with respect to the (maintained) rejections to Claims 1, 4-6, 8-19, 22-25, 27 and 32 are hereby reiterated with respect to the rejections of Claims 55, 4-6, 8-19, 22-25, 27 and 32 under 35 U.S.C. §103(a). Accordingly, Applicants respectfully submit that the rejections of Claims 55, 4-6, 8-19, 22-25, 27 and 32 under 35 U.S.C. §103(a) are overcome.

The Obviousness-Type Double Patenting Rejections

Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 13-18 of U.S. Patent No. 5,208,020 to Chari et al. in view of Hudziak in view of Lewis. Applicants note that Claim 1 has been canceled.

However, as U.S. Patent No. 5,208,020 to Chari is not assigned to Genentech, Inc., one of the assignees of the present application, it is believed that this rejection may not properly be treated as an obviousness-type double patenting rejection. However, Applicants traverse this rejection for at least the reason that the present claims are not obvious over Chari in view of Hudziak in view of Lewis.

As discussed above, Chari fails to discuss or suggest determining whether a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody

which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells. Chari does not discuss an anti-ErbB2 antibody which has a growth inhibitory effect on SK-BR-3 cells. Hudziak and Lewis fail to provide these missing teachings. Accordingly, the combination of the cited references failing to provide the elements of the claimed invention, providing no suggestion or motivation to combine to so provide these elements, and failing to provide any reasonable expectation of success if such a combination were made, Applicants submit that the cited references fail to make Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 obvious and that the claim rejections under 35 U.S.C. §103(a) are overcome.

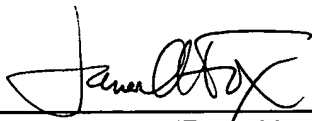
CONCLUSION

Applicants respectfully submit that all claims stand in allowable form, and respectfully request their reconsideration and allowance. Early notification of the allowance of all claims is respectfully requested.

Please charge the fee for a three month extension of time, and any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641, referencing Attorney's Docket No. 39766-0073 A2.

Respectfully submitted,

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